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UNITED STATES DISTRICT COURT

NORTHERN DISTRICT OF CALIFORNIA, SAN FRANCISCO DIVISION

GUARDANT HEALTH, INC.,

Plaintiff and Counterclaim-Defendant,

vs.

NATERA, INC,

Defendant and Counterclaim-Plaintiff.

Case No. 21-cv-04062-EMC

NATERA'S MOTION *IN LIMINE* NO. 3 TO EXCLUDE EVIDENCE OF, OR ARGUMENT REGARDING, CERTAIN PUBLISHED OR UNPUBLISHED STUDIES REGARDING SIGNATERA®

Pretrial Conference:
Date: June 28, 2023
Time: 3:00 pm
Ctrm: 5 – 17th Floor
Judge: Hon. Edward M. Chen

Trial:
Date: July 24, 2023

[redacted]

I. INTRODUCTION

Natera moves *in limine* under Federal Rules of Evidence 402 and 403 to exclude evidence of or argument regarding the following confidential pilot trials and later-published studies regarding Signatera®:

- Certain confidential "bakeoff" pilot trials by third-party biopharma companies that were never published or peer-reviewed ("Third-Party Bakeoffs");
- A study by Henriksen *et al.* published in February 2022 ("Henriksen I")[1];
- A study by Henriksen *et al.* published in August 2022 ("Henriksen II")[2]; and
- A study by Fakih *et al.* published in March 2022 ("Fakih").[3]

None of these items has any probative value to any issue to be decided at trial. In all of the at-issue advertising, Natera cited then-existing published studies such as the Reinert[4] and CIRCULATE studies to support Natera's description of Signatera's performance. Natera did not rely on any unpublished "Third-Party Bakeoffs," nor on any of the later-published Henriksen I, Henriksen II, and Fakih studies. Presenting these irrelevant studies at trial would unnecessarily cause jury confusion and undue delay in an already complex trial.

Additionally, Natera moves *in limine* to exclude all evidence or argument seeking to attack the Reinert study as allegedly unreliable, fraudulent, or otherwise conducted in an improper manner. The Court has already rejected Guardant's unclean hands defense on summary judgment (Dkt. 326 at 42-43), and there is no other basis for or relevance to such attacks.

II. ARGUMENT

A. The Court should exclude evidence or argument regarding confidential and unpublished Third-Party Bakeoffs.

Guardant has repeatedly sought to inject unpublished, confidential Third-Party Bakeoffs into

[1] Henriksen *et al.*, Circulating Tumor DNA in Stage III Colorectal Cancer, beyond Minimal Residual Disease Detection, toward Assessment of Adjuvant Therapy Efficacy and Clinical Behavior of Recurrence, *Clinical Cancer Research* (2022), 28, 507 (Ex. 24) (also cited as Ex. 754).
[2] Henriksen *et al.*, Comparing single-target and multitarget approaches for postoperative circulating tumor DNA detection in stage II-III colorectal cancer patients, *Molecular Oncology* (2022), 16, 3654 (attached as Ex. 25) (also cited as Ex. 1405).
[3] Fakih *et al.*, Evaluation of Comparative Surveillance Strategies of Circulating Tumor DNA, Imaging, and Carcinoembryonic Antigen Levels in Patients With Resected Colorectal Cancer, *JAMA Network Open* (2022), 5(3), e221093 (attached as Ex. 26) (also cited as Ex. 1210).
[4] Reinert *et al.*, Analysis of Plasma Cell-Free DNA by Ultradeep Sequencing in Patients with Stage I to III Colorectal Cancer, *JAMA Oncology* (2019), 5(8), 1124 (attached as Ex. 27).

[redacted]

this litigation. However, those exploratory, pilot trials have no bearing on any of the parties' claims or defenses, as they were not relied on by either party in any advertising at issue. *See* Fed. R. Evid. 401, 402. Nor are the Third-Party Bakeoffs admissible—their results are pure hearsay not subject to any exception. *See* Fed. R. Evid. 801, 803. Even setting aside these issues—either one of which justifies exclusion on its own—any minimal probative value the bakeoff trials may be argued to have is substantially outweighed by the high risk of jury confusion, undue delay, and undue prejudice to Natera, if they were to be admitted as evidence at trial. *See* Fed. R. Evid. 403.

Third-Party Bakeoffs are feasibility programs sponsored by private third-party pharma companies that tested non-clinical samples using different ctDNA assays. They are not research studies in the way the Reinert study or even the Parikh study were—they are neither published or peer-reviewed, nor intended to be shared publicly. The participants have only limited involvement: typically they are provided samples, run them, and then return the results to the pharma company, who in turn analyzes the results and determines the outcome. By design, very limited information is shared with bakeoff participants, and their identities are typically even shielded from one another.[5] Unlike public research studies, the Third-Party Bakeoff trials are intended for one audience only—the pharma company conducting them.

[redacted] This confidential bakeoff (the second of two involving Natera and Guardant) presents numerous factual issues that make it misleading and confusing, and not what Guardant purports it to be—proof that Reveal performed better than Signatera. [redacted] Ex. 28 (Metzker Rbt. Rpt.) at ¶ 53 & n.122 (citing Guardant documents); Ex. 10 (GHI00014505) at 508-10. [redacted]. Ex. 29 (GHI00013010) at 010. [redacted]

[5] For example, by identifying the participating vendors as Vendors A, B, and C rather than by their names or the names of their respective tests.

[redacted]

[redacted] Ex. 30 (GHI00006666) at 666; Ex. 31 (GHI00006536) at 536. [redacted] Ex. 8 (GHI00013035) at 035.

[redacted] Ex. 32 (NATERA_006900) at 900. [redacted]. To this day, Natera is unaware of what Guardant was doing behind the scenes in connection with this bakeoff pilot trial, including that [redacted] Introducing this irrelevant and inadmissible bakeoff into evidence would require a lengthy mini-trial on the subject of bakeoffs, their purpose and limitations, and the specific factual issues presented by [redacted] This would take away from presentation time that should be spent on issues that are actually relevant to the case, and would confuse and mislead the jury. The prejudice to Natera would be severe and, with no [redacted] witness to question at trial, nearly impossible to cure.

It is worth noting that the Third-Party Bakeoffs at issue here also implicate third-party confidential information that neither Natera nor Guardant has the right to unilaterally share at trial. Natera will object to any attempt by Guardant to use this public trial as a means of publicizing any confidential Third-Party Bakeoff. Natera has reason to be concerned about this, given that Guardant's CEO Dr. Eltoukhy has made public statements about Guardant's purportedly superior performance in Third-Party Bakeoffs, including at the January 2022 JP Morgan Healthcare conference, despite the data being confidential and his statements being highly misleading given how Guardant conducted itself in the bakeoffs. *See* Dkt. 122-2 at 27. In discovery, Natera learned Dr. Eltoukhy also [redacted] Ex. 2 (Eltoukhy Dep. Tr.) at 306:25-320:25.

For all these reasons, the Court should exclude all evidence and argument regarding Third-Party Bakeoffs, [redacted].

[redacted]

B. The Court should exclude evidence or argument regarding the later-published Henriksen I, Henriksen II, and Fakih.

Each of Henriksen I, Henriksen II, and Fakih was published in 2022, ***several months after*** the initiation of this lawsuit and well after the at-issue advertising statements. *See* Ex. 24, 25, 26. Natera's marketing statements at issue—all from 2021—are based on the peer-reviewed Reinert study that was published in 2019 (Ex. 27); none of Natera's at-issue advertising cites or relies on Henriksen I, Henriksen II, or Fakih. *See* Dkt. 1 at ¶¶ 25-35; Ex. 33 (Heitjan Op. Rpt.) at ¶ 53. The same is true of Guardant's advertising—none of it cites or relies on Henricksen I, Henriksen II, or Fakih. Indeed, none of these studies were published as of 2021 when the disputed advertising was created, and thus these later publications could not have been known to either party when the alleged false advertising happened. Henriksen I, Henriksen II, and Fakih are thus plainly irrelevant to any issue of consequence for trial. *See* Fed. R. Evid. 401, 402.

For the additional reasons given below, the Court should also exclude evidence of or argument concerning these later-published studies, as each one—if presented at trial—will inevitably cause jury confusion and undue delay. *See* Fed. R. Evid. 403.

1. Henriksen I

Henriksen I was published in *Clinical Cancer Research* in February 2022, ***over eight months*** after the initiation of this lawsuit in May 2021 and well after the at-issue advertising. *See* Ex. 24. Although it has some overlapping authors with Reinert, Henriksen I is a later published, different study evaluating different patients. *See* Ex. 24, 27. Guardant will likely use this irrelevant study for several irrelevant and prejudicial purposes at trial. *See* Fed. R. Evid. 403.

First, Guardant will likely use Henriksen I to argue [redacted] Dkt. 249-02 at 24-25. Guardant's objective with these arguments is to create false equivalence between Natera's proper conduct over the course of two ***different*** studies (Reinert and Henriksen I, published years apart), and Guardant's secretive, behind-

the-scenes manipulations within the Parikh study before its publication.

Importantly, any such argument is irrelevant to any claims or defenses because none of the at-issue advertising relies on or even cites the later-published Henriksen I. Nor does any of the work done for Henriksen I have any relevance to the previously published Reinert study. As noted, Natera's description of Signatera's performance in its 2021 marketing statements was based on Reinert that had been peer-reviewed and published in 2019, ***years before*** any data analysis for Henriksen I, and thus any subsequent data analysis in Henriksen I does not and cannot change the published results of Reinert that Natera relied on in its advertising. Guardant attempts to use Henriksen I to obfuscate and to confuse the jury about Guardant's improper conduct in Parikh, where Guardant reanalyzed data after being unblinded to clinical outcome ***in the middle of*** the study to artificially improve the study results before the publication of the Parikh study. If Guardant were allowed to make these tangential and unfounded arguments regarding the irrelevant Henriksen I at trial, then Natera must present its own witnesses to disprove Guardant's specious arguments, which will cause significant undue delay and risk jury confusion.

Second, Guardant has tried to use Henriksen I to cast doubt on the Signatera 8.7-month lead time Natera advertises based on Reinert. *See* Dkt. 249-02 at 16 (arguing that Signatera "only detected ctDNA before recurrence in a third (6 of 18) of cases"); Ex. 35 (Sharma Dep. Tr.) at 170:2-197:23 (questioning Natera's fact witness at length about lead time and Henriksen I). But Henriksen I, a peer-reviewed publication, explicitly reports a lead time of 9.8 months, Ex. 24 at 507, which is consistent with the 8.7-month lead time reported by Reinert, another peer-reviewed publication. Guardant's attempt to invite the jury to reanalyze the published lead-time results of two papers should be rejected.[6] Any minimal probative value (if any) is substantially outweighed by the high risk of jury confusion and undue delay. Therefore, the Court should exclude all evidence and arguments regarding Henriksen I.

[6] Guardant has also cited a 3.4 ng/mL CEA threshold applied to certain Spanish patients in Henriksen I, in its attempt to justify the Parikh study's use of a 3.4 ng/mL CEA threshold. Dkt. 224-02 at 13. This issue is moot because Natera does not intend to raise the CEA threshold at trial.

[redacted]

2. Henriksen II

Henriksen II was published in *Molecular Oncology* in August 2022, ***over fourteen months*** after the initiation of this lawsuit and even further removed in time than Henriksen I to Natera's 2021 marketing statements. Henriksen II compares two different tumor-informed ctDNA detection approaches: (1) a single-target (ST) droplet digital PCR (ddPCR) approach, and (2) a multi-target (MT) multiplex-PCR next generation sequencing (Signatera) approach. Ex. 25 at 3654-55. Thus, Henriksen II involves a ***third*** technology for ctDNA detection (ddPCR) that differs from both Signatera and Reveal, and ddPCR is neither at issue nor relevant here. Introducing Henriksen II into evidence would require Natera to present witnesses to explain the various ctDNA detection approaches, as well as the study design and data analysis of a later publication that was not (and could not have been) cited or relied upon by any of the at-issue advertising.

Guardant is using Henriksen II to support its baseless attack of Signatera's performance. Guardant and its technical expert Dr. Heitjan have cited Henriksen II for its reported 4.1-month lead time and 10/22 post-surgery recurrence detection rate. *See* Dkt. 249-02 at 16; Ex. 34 (Heitjan Rbt. Rpt.) at ¶ 26. But these isolated numbers taken from the later-published Henriksen II are not relevant or probative to whether Natera's *2021* advertising statements *based on Reinert*, peer-reviewed and published in 2019, are truthful or false/misleading. Henriksen II does not and cannot change the results of the studies that Natera actually relied upon in its 2021 advertising. But the jury may be confused into giving more weight to Henriksen II because it is a newer study. Any possible probative value would be minimal at best and substantially outweighed by the high risk of jury confusion and undue delay. The Court should therefore exclude all evidence and arguments regarding Henriksen II.

3. Fakih

Fakih was published in *JAMA Network Open* in March 2022, ***over nine months*** after the initiation of this lawsuit and well after the at-issue marketing statements. Fakih is a retrospective, single-center study, and it is unrelated to the Reinert study. Ex. 26 at 1. Guardant and its expert Dr. Heitjan have cited Fakih to argue that Signatera "was less sensitive than imaging combined with CEA blood tests, and provided no lead time advantage in detecting recurrence." Dkt. 249-02 at 16;

[redacted]

Ex. 33 (Heitjan Op. Rpt.) at ¶¶ 58(8), 77. But Dr. Heitjan's opinions on Fakih are unreliable, as he has admitted that he did not even "read the whole thing." Ex. 3 (Heitjan Dep. Tr.) at 194:1-12. Admitting Fakih into evidence would require Natera to present witnesses to address this later-published study that was never cited or relied upon in the at-issue advertising. This will needlessly cause undue delay and jury confusion at trial. *See* Fed. R. Evid. 403. Any conceivable probative value would be minimal and substantially outweighed by the high risk of jury confusion and undue delay; the Court should exclude all evidence and arguments regarding Fakih.

C. The Court should exclude evidence or argument attacking the Reinert study as allegedly unreliable, fraudulent, or otherwise improper.

Lastly, Natera moves to exclude all evidence or argument that seeks to attack the Reinert study as allegedly unreliable, fraudulent, or otherwise conducted in an improper manner.

In its Complaint, Guardant did not allege the Reinert study was in any way false, misleading, or unreliable. *See* Dkt. 1. Nor did it allege that Natera falsely advertised based on Reinert. It was only ***after*** Natera identified in its counterclaims serious flaws with the Parikh study and Guardant's behind-the-scenes manipulation, and those counterclaims survived Guardant's motion to dismiss, that Guardant alleged the Reinert study was fraudulent and unreliable as part of its unclean hands defense. *See* Dkt. 131-2 at 84-85.

The Court has now rejected Guardant's unclean hands defense on summary judgment. *See* Dkt. 326 at 42-43. In particular, the Court held that [redacted] *Id*. As such, any related evidence and argument attacking the Reinert study as unreliable, fraudulent, or otherwise improper, is irrelevant and should be excluded from trial to avoid undue prejudice to Natera, confusing the jury, and undue delay of the trial.

III. CONCLUSION

For at least the reasons stated above, Natera's motion *in limine* should be granted.

[redacted]

DATED: May 26, 2023

Respectfully submitted,

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UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF CALIFORNIA
SAN FRANCISCO DIVISION

GUARDANT HEALTH, INC.,

Plaintiff,

vs.

NATERA, INC.,

Defendant.

Case No. 3:21-cv-04062-EMC

PLAINTIFF GUARDANT HEALTH, INC.'S RESPONSE IN OPPOSITION TO NATERA'S MOTION IN LIMINE NO. 3 TO EXCLUDE EVIDENCE, OR ARGUMENT REGARDING, CERTAIN PUBLISHED OR UNPUBLISHED STUDIES REGARDING SIGNATERA

Pretrial Conference:
Date: June 28, 2023
Time: 3:00 p.m.
Place: Courtroom 5

Guardant Health, Inc. (Guardant) opposes Natera's Motion *in Limine* No. 3 to exclude evidence or argument regarding certain studies involving Signatera ("Natera MIL No. 3").

I. INTRODUCTION

Natera's request that the Court bar evidence and arguments concerning

- [redacted] compared the performance of Signatera and Reveal;
- Three studies cited by Guardant's expert Dr. Daniel Heitjan as a basis for his opinions, including
  - A peer-reviewed study published in 2022 by Natera and its Danish co-authors evaluating Signatera in a cohort of patients that included patients from the Reinert Study (Henriksen I)[2];
  - A peer-reviewed study published in 2022 by Natera's Danish collaborators (but not involving Natera) evaluating Signatera in a cohort of patients also included in the Reinert Study and Henriksen I Studies (Henriksen II)[3];
  - A 2022 peer-reviewed study of Signatera led by Dr. Marwan Fakih at the City of Hope Hospitals in California; [4]
- The 2019 Reinert Study, co-authored by, relied upon and cited by Natera in its Signatera advertising;

should be denied. Evidence concerning these studies is highly relevant to Guardant's false advertising claims against Natera and will be used to explain to the jury why Natera's apples-to-oranges comparisons of Reveal and Signatera are unfair, and thus false and misleading. Moreover, Guardant is entitled to probe what Natera meant when it described the Reinert Study as a "prospective" and "blinded," and how these definitions square with arguments made by Natera's experts and trial counsel concerning the use of these terms in the Parikh Study.

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[1] Natera's MIL No. 3 does not describe [redacted]

[2] Henriksen *et al.*, Circulating Tumor DNA in Stage III Colorectal Cancer, beyond Minimal Residual Disease Detection, toward Assessment of Adjuvant Therapy Efficacy and Clinical Behavior of Recurrence, *CCR* (2022), 28, 507 (Ex. 24 to Natera's MIL No. 3).

[3] Henriksen *et al.*, Comparing single-target and multitarget approaches for postoperative circulating tumor DNA detection in stage II-III colorectal cancer patients, *Molec. Onc.* (2022), 16, 3654 (Ex. 25 to Natera's MIL No. 3).

[4] Fakih *et al.*, Evaluation of Comparative Surveillance Strategies of Circulating Tumor DNA, Imaging, and Carcinoembryonic Antigen Levels in Patients With Resected Colorectal Cancer, *JAMA Network Open* (2022), 5(3), e221093 (Ex. 26 to Natera's MIL No. 3).

II. ARGUMENT

A. Natera's Participation in Third Party "Bake-offs" Using Signatera and Its Knowledge of the Results Are Highly Relevant

There is no dispute that Guardant and Natera [redacted]. Ex. 1432 Odegaard Dep. at 316:25-317:11; Ex. 1433, Aleshin Dep. at 30:21-31:6; 31:24-32:5, 33:1-9; 35:1-5. [redacted] Ex. 1433 at 98:9-16. [redacted] *E.g.*, Ex. 1434 NATERA_260962 and 260973 [redacted] Ex. 172, Ex. 1433 at 51:15-52:6, 52:18-21.

Mischaracterizing the bake-offs' relevance, Natera argues that Guardant intends to use this evidence as proof that "Reveal performed better than Signatera," and claims the data does not support this conclusion. (Natera MIL No. 3 at 2-3). Natera can offer these arguments to the jury; they do not support a conclusion that the bake-offs are "irrelevant." In fact, the bake-offs are highly relevant to issues that go beyond the simple question of which assay "performed better."

1. [redacted] Prove Natera Knew That Plasma Only MRD Assays Could Provide Equivalent or Superior Sensitivity to Tissue Informed Assays

Even before Guardant launched Reveal, [redacted] Ex. 127, NATERA_230766 (Nov. 26, 2019), forwarding Ex. 128, NATERA_230768 (Signatera CRC field deck). In fact, [redacted] *Id.* at NATERA_230785. Natera also told its sales team: [redacted] *Id.* at NATERA_230787.

But Natera already knew this representation was untrue. As Natera admitted after reviewing

the results of the [redacted] While Natera [redacted] *See* Ex. 172, NATERA_015589 (Feb. 19, 2019). Natera's awareness of Guardant's assay performance and its ability to predict recurrence using epigenomics preceded Natera's false advertising campaign targeting Reveal and is relevant to show that Natera's false advertising was "knowing" and/or "willful."

2. Natera's Communications and Data Show that Natera Knew Signatera Exhibited Degraded Performance With Low Sample Volumes

With regard to the second (2019) bake-off using presurgical plasma samples, the documents produced by Natera show that [redacted] *see* Ex. 197 & 198 NATERA_007439 & 007441; Ex. 1434, GHI00042448 and GHI00042449 [redacted]. *See* e.g., Ex. 196, NATERA_014775 [redacted] These data show that [redacted] Ex. 1436, NATERA_014857 [redacted] Ex. 198, NATERA_007441 [redacted] Nonetheless, Natera compared Signatera and Reveal's presurgical sensitivity in its advertising, despite the Parikh Study's express limitation that "all of our samples had plasma input volumes of 4 mL or less, versus the recommended input of 8-10 mL." Ex. 2 (Parikh Study) at 5592.

3. The Bakeoff Results Produced By Each Party Are Not "Hearsay"

Both Natera and Guardant produced communications and data about the bake-offs in discovery, and both parties provided witnesses to testify about their assays' performance in the bake-offs. This evidence and testimony is not inadmissible "hearsay."

Guardant can also testify as to the accuracy of its own data as reflected in [redacted] *E.g.*, Ex. 198, NATERA_007441. Natera never disputed that this [redacted], *contra* Ex. 1436, NATERA_014857 [redacted]), and its failure to object to its accuracy constitutes an adoptive admission. FED. R. EVID. 801(d)(2)(B); *U.S. v. Schaff*, 948 F.2d 501, 505 (9th Cir. 1991) ("Silence in response to the statement of another is an adoptive admission under Rule 801(d)(2)(B) if the district court makes a determination that, under the circumstances, an innocent defendant normally would respond to the statement.") Although a third vendor's "(Vendor C") data in these documents might be hearsay if offered for its truth, Guardant does not intend to comment or make arguments about this data at trial.

4. "Confidentiality" Does Not Bar Guardant From Presenting Evidence From [redacted] To A Jury

Natera does not identify what "third-party confidential information" is purportedly "implicated" by [redacted] (Natera MIL No. 3 at 3), explain why this information is "confidential," or cite any authority that "confidentiality" can be a basis for excluding otherwise relevant evidence from use at trial. Guardant reiterates its agreement to redact data from [redacted] from any exhibit used at trial. Otherwise, all documents concerning the [redacted] were produced by either Natera or Guardant, and not any other third party; and Guardant is unaware that any third party has objected to their use at trial.

B. The Henriksen I, Henriksen II and Fakih Studies Are Relevant

Natera's request to exclude evidence about the Henriksen I, Henriksen II and Fakih Studies—which were cited by Guardant's expert, Daniel Heitjan in his expert report[5]—should also fail. Natera's objections that these studies were published too late, describe irrelevant technologies, and were not cited in its advertising, misstate their relevance, and do not justify exclusion.

[5] Natera's untimely challenge to Dr. Heitjan's opinion, Natera MIL No. 3 at 7 ("Dr. Heitjan's opinions on Fakih are unreliable"), must be rejected. Per the Court's scheduling order (Dkt. 208, 213), *Daubert* challenges to expert testimony, which includes challenges to its reliability, were due on October 14, 2022. Natera did not challenge ***any*** of the opinion testimony offered Dr. Heitjan. Natera is foreclosed from raising this challenge now.

1. Natera's Attempts to Revise the Data and Conclusions in Henriksen I Were Part of its [redacted]

After Natera and its Danish collaborators published the Reinert Study in 2019, they used a subset of this same data with data from additional patients from Spain to prepare a second paper which became Henriksen I. Ex. 24 to Natera MIL No. 3 at 508 (describing subjects). Although not published until 2022, Natera was working on Henriksen I when it learned of Reveal's impending launch in early 2021. Natera's communications with its Danish collaborators about Henriksen I show the depths of Natera's concerns that [redacted] Ex. 436, NATERA_441662 [redacted] *See also* Ex. 137, NATERA_320165 (Feb. 10, 2021) (S. Moshkevich) [redacted] Ex. 772, NATERA_28812 [redacted]

2. Henriksen I and II Illustrate Why Signatera's Claim of a Diagnostic Lead Time Advantage Over Reveal Is False

Fairly comparing the diagnostic lead times of different ctDNA assays requires measuring "time to recurrence" from a common starting point. Ex. 1412 (Heitjan Report) at 21. Using data first reported in the Reinert Study, both Henriksen I and II re-evaluated the diagnostic lead time of Signatera using the first positive ctDNA result *after definitive therapy* as a starting point. This is the [redacted], Ex. 306, (NATERA_350886), but different from the starting point used in the Reinert Study (which measured lead time from the first post-operative ctDNA positive result). Both studies show that the choice of starting point makes a significant difference in the reported lead time. In Henriksen I the authors reported that "during surveillance after end of definitive treatment, the median lead-time of ctDNA [of Signatera] was 6 months," Ex. 24 to Natera MIL No. 3 at 512. However, if positive samples "detected prior to the conclusion of [adjuvant therapy] are included, the median lead-time increases to 10 months. *Id*. Likewise, in Henriksen II,

the authors reported that Signatera provided a median diagnostic lead time using surveillance samples after end of definitive treatment of 4.1 months. Ex. 25 to Natera MIL No. 3 at 6. This lead time is less than half of the 8.7 months claimed by Natera in its Reveal Performance Comparison and equivalent to the "≈4 month" lead time Natera ascribed (falsely) to Reveal. *See* Signatera vs Reveal Performance comparison. Ex. 306, NATERA_350886. As Guardant's expert explains, [redacted] Ex. 1412 (Heitjan Expert Report) at 26, and illustrate why Natera's lead time comparison is literally false.

3. The Fakih Study Further Illustrates How Blood Draw and Scanning Schedules Impact Diagnostic Lead Time Estimates

Fairly comparing the diagnostic lead times of different ctDNA assays also requires using common schedules for ctDNA draws and follow-up CT imaging. Ex. 1412 (Heitjan Report) at 21; Ex. 1437, NATERA_297796 at 297801 (noting that [redacted] A 2022 study led by Dr. Marwan Fakih and published in JAMA Oncology (the *Fakih* Study, Ex. 26 to Natera MIL No. 3) shows how blood draw and imaging schedules impact diagnostic lead time estimates and is cited by Guardant's Expert, Dr. Daniel Heitjan for this reason.

In the Fakih Study, the investigators posited that the Reinert Study's finding that Signatera "identified disease recurrence at a median of 8.7 months before radiographic recurrence" "should be viewed "in the context of the surveillance frequency of imaging studies." *Id*. Noting that Danish cancer guidelines that call for "post-operative radiographic imaging at 1 and 3 years are considered substandard in the US," the researchers evaluated Signatera's diagnostic lead-time using a protocol that called for yearly CT scans for low-risk stage II cancer patients and scans every 6 months for high-risk stage II and III patients. *Id*. In this context, the researchers found that Signatera provided *no* diagnostic lead time compared to CT scans. *Id*. *See also* Ex. 1412 (Heitjan Expert Report) at 26 (citing Fakih Study as "cast[ing] doubt on whether Signatera provides any advantage at all over standard-of-care imaging in monitoring for colorectal cancer recurrence.")

C. Natera's Conduct During and After the Reinert Study Is Relevant as Impeachment Evidence

While Guardant does not need to show that the Reinert Study is "unreliable, fraudulent, or

otherwise conducted in an improper manner," to prevail on its false advertising claims against Natera, Guardant is entitled to present the jury with evidence of the wildly inconsistent positions Natera has taken concerning the meaning of "prospective" and "blinded," when used in the context of a clinical study. These include the differences between Natera's use of these terms to describe its studies of Signatera, and the arguments its experts and trial counsel have made during the course of this litigation. For example, and just like the authors of the Parikh Study, the Reinert Study authors describe their study as "prospective," Ex. 12 (Reinert Study) at 1124 ("In this prospective multicenter cohort study. . . ") even though [redacted]

Likewise, the Reinert Study describes the ctDNA analysis performed by Natera as having been performed "blinded to clinical outcome," [redacted]. 752, NATERA_027196 at 197 (Mar. 27, 2018); Ex. 755, NATERA_080253 (Apr. 2, 2018). [redacted]. 759, NATERA_101763 [redacted] Ex. 760, NATERA_103204 (May 4, 2018). [redacted] Natera's descriptions of its own studies at least undermine its arguments that the Parikh Study is "falsely" described as a "prospective" and "blinded" study. The jury should be allowed to consider this evidence and argument, which is not unfairly prejudicial nor subject to exclusion under Rule 403. *U.S. v Hankey*, 203 F.3d 1160, 1172 (9th Cir. 2000) ("Relevant evidence is inherently prejudicial, but it is only unfair prejudice, substantially outweighing probative value which permits exclusion of relevant matter.") (quoting *United States v. Mills,* 704 F.2d 1553, 1559 (11th Cir.1983).

III. CONCLUSION

As set forth above, Guardant requests that the Court ***DENY*** Natera's MIL No. 3.

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